Suntanning with p53

The cutaneous response to ultraviolet (UV) radiation involves α-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone in melanocytes. UV tends to induce specific mutations in the p53 tumor suppressor gene, and the p53 protein is also essential for the formation of "sunburn cells." Cui and colleagues recently demonstrated that p53 actually plays a crucial role in the suntan response of melanocytes. UV treatment of skin resulted in upregulation of the gene encoding α-MSH (*POMC*) as well as in p53 induction. *POMC* was a direct transcriptional target of p53. In support of these molecular findings, mice deficient in p53 exhibited deficient tanning in response to UV. Interestingly, other p53 inducers, such as 5-fluorouracil, ionizing radiation, or oncogenesis, often result in hyperpigmentation. Thus, p53 functions as a UV sensor and effector to transcriptionally activate the melanocyte pigmentation pathway. (*Cell* 128:853–64, 2007)

Long fatty acids form the barrier

A functional epidermal permeability barrier depends on the extracellular domains of the stratum corneum, which consists of a hydrophobic lipid mixture of free fatty acids, cholesterol, and ceramides. Mutations in the elongation of very-long-chain fatty acids (ELOVL4) are associated with Stargardt-like macular degeneration. Because this gene is also expressed in the skin, Vasireddy and colleagues examined mice with these mutations for defects in epidermal function. The mice exhibited scaly wrinkled skin, compromised epidermal permeability function, deficient epidermal lamellar body content, and impaired survival in the hours following birth. In addition, a significant decrease in very-long-chain fatty acids and a lack of epidermal ω-*O*-acylceramide and its immediate precursor were also noted. The results clearly demonstrate that ELOVL4 is required not only for generation of very-long-chain fatty acids that are critical for epidermal barrier formation but also for mammalian survival. (*Hum Mol Genet* 16:471–82, 2007)

Rac1 for wound healing

A few intracellular signaling molecules have previously been identified in wound re-epithelialization. One of these—signal transducer and activator of transcription 3 (STAT3)—is directly regulated by the GTP-binding protein Rac1. Recently, Tscharntke and colleagues examined the effects of a dominant negative form of this protein in basal epidermal keratinocytes using the keratin 14 promoter in mice. Although no overt skin phenotype was noted in the transgenic animals, a dramatic delay of wound re-epithelialization was noted at days 2 and 5 following wounding. The findings were confirmed following epidermis-specific deletion of *Rac1*. In the absence of Rac1, keratinocytes exhibited decreased proliferation, less efficient attachment and spreading, reduced lamellipodia protrusion, and reduced migration. The observations provide a molecular characterization of the defective wound healing in these animals. Thus, the results demonstrate that in epidermal keratinocytes, Rac1 is integral for efficient wound re-epithelialization. (*J Cell Sci* 120:1480–90, 2007)

Alternative splicing ENCODEs diversity

The Encyclopedia of DNA Elements (ENCODE) was developed to identify all functional elements in the human genome. In a pilot project, 44 selected regions, which comprise 1% of the genome and contain 2,608 annotated transcripts for 487 distinct loci, have been comprehensively analyzed. In a recent study of the dataset, Tress and colleagues explored the frequency and functional significance of alternative premessenger RNA splicing, a process that enables genes to generate multiple gene products and theoretically increases the functional complexity of the genome without necessitating increased numbers of genes. Alternative splicing was identified at 57.8% of the loci. Splicing variants included deletions and insertions of exons as well as C-terminus substitutions. Splicing alters signal peptides as well as transmembrane helices. Although splicing events affect functional domains, these events occur most often within domains and may drastically alter the structure and function of the proteins. Taken together, the findings suggest that alternative splicing is commonplace and contributes to the creation of new protein functions; however, these dramatic changes may be more revolutionary than evolutionary. (*Proc Natl Acad Sci* 104:5495–500, 2007)

Lipid triggers in wound healing

Although growth factors and cytokines are clearly involved in triggering an inflammatory response during wound healing, bioactive lipids, such as sphingosine-1-phosphate (SIP), contribute by mediating further inflammation, cell growth, and tissue development. Specifically, SIP spearheads a signaling cascade that results in nuclear translocation of the LIM-only protein Fhl2, which ultimately interacts with transcription factors. Therefore, Wixler and colleagues examined the role of Fhl2 in mesenchymal cells during wound healing. Fhl2 was found to be responsible for nonredundant signaling during wound healing. Fhl2-deficient mice exhibited delayed wound healing, reduced migration of mesenchymal precursor cells, delayed activation of α-smooth muscle actin, and defective wound contraction. These results link the release of the bioactive lipids SIP and lysophosphatidic acid from platelets during clotting and wound healing with wound contraction by granulation tissue. (*J Cell Sci* 177:163-72, 2007)

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